REMARKS

Reconsideration of the rejection of all claims is respectfully requested in view of the above amendments and the following remarks.

Claim Amendments

Independent claims 10, 12, 13, 17 and 18 have been amended, as suggested by the Examiner, by inserting the chemical name of AZD2171 in parentheses following the first citation of AZD2171. Support for this amendment is found in the specification, *e.g.*, at page 3, lines 3-4.

Claim 22 has been amended as requested by the Examiner to read, in part, "selected from the group consisting of."

Claim 22 has designated as "withdrawn" as requested by the Examiner in view of the provisional election of the species "docetaxel."

It should be clear from the above that no new matter has been added by these amendments, and entry there of is respectfully requested. Moreover, these amendments may provide an extra measure of clarification but are not intended to change the scope of the claims in any respect.

Status of the Claims

Following entry of the above amendments, claims 10 and 12-24 remain in this application, with claims 10 and 19-23 currently being in active prosecution.

Method (process for using) claims 12-18 are designated as withdrawn, and the composition recitations therein have been amended in a manner consistent with composition claim 10 so as to be ready for rejoinder upon allowance of claim 10.

Composition claim 24 falls within elected Group I, but has been designated as withdrawn pursuant to the provisional election of species, with the expectation that the claimed composition with paclitaxel will be examined when the composition with the elected species, docetaxel, is found allowable.

Objection

The objection to claim 22 has been overcome by the insertion of "the group consisting of" as requested by the Examiner, in order to expedite the prosecution of this application.

Claim rejections - 35 USC 112 - Second Paragraph

Claims 10 and 19-23 have been rejected as being indefinite on the assertion that claims 10, 19, 20 and 21 fail to state the full meaning of the term "AZD2171" at the first occurrence of that term in those claims. While Applicants believe that the full meaning of such term is clearly, definitely and unambiguously established by the specification, in order to expedite the prosecution of this application to allowance claim 10 has been amended by inserting the full chemical name of AZD2171 in parentheses following the first recitation of "AZD2171" in that claim. It is respectfully submitted that it is unnecessary to amend dependent claims 19, 20 and 21 inasmuch as they necessarily incorporate the full definition of this term from independent claim 10. Presently withdrawn independent method claims 12, 13, 17 and 18 have been amended in the same manner so as to be in condition for rejoinder upon allowance of a composition claim.

It is therefore believed that this ground for rejection has been overcome, and its withdrawal is respectfully requested.

Claim rejections - 35 USC 102

Claims 10 and 19-23 are rejected under 102(b) as being anticipated by Stokes *et al.*, WO 00/47212 (hereinafter "Stokes WO '212"), which the Examiner notes corresponds to US Patent 7,074,800 (hereinafter "Stokes US '800"), to which the Examiner primarily refers in the statement of this rejection. In support of this anticipation rejection, the Examiner notes at page 4 of the Action that Stokes US '800 "teaches combinations comprising certain angiogenesis inhibitors, including AZD2171, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable excipient or carrier," specifically pointing to "reference claims 12, and 25." With respect to the taxane component of the present claims, the Examiner further asserts at page 5 of the Action:

> In particular, "Stokes et al. disclose antiproliferative/antineoplastic agents such as taxoid like taxol and taxotere (also known as docetaxel) to be suitable for use in combination with said antiangiogenic compounds (col. 63, lines 11-32, especially line 23). The following terms overlaps with the teaching of Stokes et al.: "a taxane" as recited in claim 10; "docetaxel" as recited in claims 22 and 23.

This ground for rejection is respectfully traversed. It is submitted that there is no disclosure of the in Stokes *et al.* of any combination of AZD2171 and a taxane. Stokes *et al.* comprises a

generic teaching that *any* of a vast number of generically disclosed or specifically named angiogenesis inhibitors may be combined with *any* of a vast number of generically disclosed or specifically named chemotherapeutic agents. No preference is expressed for any particular angiogenesis inhibitor *to use in such a combination*, and the *only* preference with respect to the *other* agent of such a combination is at column 63, lines 34-39, noting a combination of the vascular targeting agent N-acetylcolchinol-O-phosphate (which clearly is not a taxane) with "a compound of formula I as defined hereinbefore."

Individually AZD2171 is one of the compounds falling within the generic scope of compounds of formula I in Stokes *et al.*, and the present specification acknowledges at page 3 that AZD2171 is one of the compounds named and exemplified therein. Specifically, AZD2171 is exemplified in Example 240 (out of over 300 exemplified compounds). The Examiner notes that AZD2171 is the compound of claim 12 of Stokes US '800, but claim 12 is one of thirteen claims that name a specific different compound (claims 12-25).

The present specification further notes at page 3 that it is stated in Stokes WO '212 that compounds of their inventions: "may be applied as a sole therapy or may involve, in addition to a compound of the invention, one or more other substances and/or treatments," and that "such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment."

The Examiner asserts that Stokes US '800 "disclose antiproliferative/antineoplastic agents such as taxoid like taxol and taxotere (also known as docetaxel) to be suitable for use in combination with said antiangiogenic compounds," citing column 63, lines 11-32, especially line 23. However, this statement referred to by the Examiner must be considered in the context in which it is made. Thus, Stokes US '800 does list "antimitotic agents (for example vinca alkaloids like vincristine and taxoids like taxol, taxotere)" at column 63, lines 21-23 as one of many examples of "antiproliferative/antineoplastic drugs and combinations thereof" that might be used in combination with one of the compounds of formula I. However, this listing is in turn only of small portion of a much more extensive discussion of the *many* other generic and subgeneric categories of agents, and numerous agents that are specifically named by way of examples, for possible use in such conjoint treatment, as listed in Stokes US '800 as follows:

The antiangiogenic and/or vascular permeability reducing treatment defined hereinbefore may be applied as a sole therapy or may involve, in addition to a compound of the invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. In the field of medical oncology it is normal practice to use a combination of different forms of treatment to treat each patient with cancer. In medical oncology the other component(s) of such conjoint treatment in addition to the antiangiogenic and/or vascular permeability reducing treatment defined hereinbefore may be: surgery, radiotherapy or chemotherapy. Such chemotherapy may cover three main categories of therapeutic agent:

(i) other antiangiogenic agents that work by different mechanisms from those defined hereinbefore (for example linomide, inhibitors of integrin αvβ3 function, angiostatin, razoxin, thalidomide), and including vascular targeting agents (for example combretastatin phosphate and the vascular damaging agents described in International Patent Application Publication No. WO 99/02166 the entire disclosure of which document is incorporated herein by reference, (for example N-acetylcolchinol-O-phosphate));

(ii) cytostatic agents such as antioestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene, iodoxyfene), progestogens (for example megestrol acetate), aromatase inhibitors (for example anastrozole, letrazole, vorazole, exemestane), antiprogestogens, antiandrogens (for example flutamide, nilutamide, bicalutamide, cyproterone acetate), LHRH agonists and antagonists (for example goserelin acetate, luprolide), inhibitors of testosterone 5α-dihydroreductase (for example finasteride), anti-invasion agents (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function) and inhibitors of growth factor function, (such growth factors include for example platelet derived growth factor and hepatocyte growth factor such inhibitors include growth factor antibodies, growth factor receptor antibodies, tyrosine kinase inhibitors and serine/threonine kinase inhibitors); and

(iii) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as antimetabolites (for example antifolates like methotrexate, fluoropyrimidines like 5-fluorouracil, purine and adenosine analogues, cytosine arabinoside); antitumour antibiotics (for example anthracyclines like doxorubicin, daunomycin, epirubicin and idarubicin, mitomycin-C, dactinomycin, mithramycin); platinum derivatives (for example cisplatin, carboplatin); alkylating agents (for example nitrogen mustard, melphalan, chlorambucil, busulphan, cyclophosphamide, ifosfamide, nitrosoureas, thiotepa);

> antimitotic agents (for example vinca alkaloids like vincristine and taxoids like taxol, taxotere); topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan, and also irinotecan); also enzymes (for example asparaginase); and thymidylate synthase inhibitors (for example raltitrexed);
>
> and additional types of chemotherapeutic agent include:
>
> (iv) biological response modifiers (for example interferon); and
>
> (v) antibodies (for example edrecolomab).
>
> For example such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of a compound of formula I as defined hereinbefore, and a vascular targeting agent described in WO 99/02166 such as N-acetylcolchinol-O-phosphate (Exampe 1 of WO 99/02166).

(Stokes US '800 at column 62, line 36 through column 63, line 39). When considered in context it is thus clear that a taxane is just one possible agent out of an enormous listing of other agents that may be used in such conjoint treatment.

Thus, there is no disclosure in this reference of specifically selecting AZD2171 for use in a conjoint treatment as opposed to any one of the many other angiogenesis inhibitors disclosed therein; there is no disclosure in this reference of specifically selecting a taxane for use in a conjoint treatment as opposed to any one of the multitude of other chemotherapeutic agents disclosed in the above-quoted passage; and, in particular, there is *no disclosure* in this reference of *both* selecting AZD2171 *and* selecting a taxane to use *together* in such a conjoint treatment.

Very clearly, then, the disclosure of the Stokes *et al.* references do not support an anticipation rejection.

To anticipate a claim, it is not enough that a reference simply makes mention of each component of the claim in lengthy lists of alternatives. Rather, for anticipation the reference *must actually describe the claimed invention* (here the combination) in sufficient detail to place it in the hands of the skilled person. Thus, for instance, the Federal Circuit stated in *Karsten Manufacturing Corp. v. Cleveland Golf Co.*, 58 USPQ2d 1286 (Fed. Cir. 2001):

> Invalidity on the ground of "anticipation" requires lack of novelty of the invention as claimed. The invention must have been known to the art in the detail of the claim; that is, all of the elements and limitations of the claim must be shown in a single prior reference, arranged as in the claim. See C.R. Bard, Inc. v. M3 Systems, Inc., 157 F.3d 1340, 1349, 48 USPQ2d 1225, 1229-30 (Fed. Cir. 1998);

> Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).
>
> (58 USPQ2d at 1291; emphasis added).

The Federal Circuit stated again in *Elan Pharmaceuticals Inc. v. Mayo Foundation for Medical Education and Research*, 64 USPQ2d 1292 (Fed. Cir. 2002):

> The single reference must describe and enable the claimed invention, including all claim limitations, with sufficient clarity and detail to establish that the subject matter already existed in the prior art and that its existence was recognized by persons of ordinary skill in the field of the invention. Crown Operations International, Ltd. v. Solutia Inc., 289 F.3d 1367, 1375, 62 USPQ2d 1917, 1921 (Fed. Cir. 2002); In re Spada, 911 F.2d 705, 708, 15 USPQ2d 1655, 1657 (Fed. Cir. 1990) ("the reference must describe the applicant's claimed invention sufficiently to have placed a person of ordinary skill in the field of the invention in possession of it").
>
> The anticipating reference "must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter." PPG Industries, Inc. v. Guardian Industries Corp., 75 F.3d 1558, 1566, 37 USPQ2d 1618, 1624 (Fed. Cir. 1996).

(64 USPQ2d at 1296; emphasis added).

Most generally it is required that a reference actually describe the particular claimed compound or combination in order to support an anticipation rejection. However, a very narrow generic disclosure in a reference may "describe" the few compounds encompassed therein, but only where the generic formula is *so narrow* that one of ordinary skill in the art is able to "at once envisage" each the specific compound within the generic chemical formula. The classic Federal Circuit decision cited for this narrow exception to the general requirement that a reference, to be an anticipation, must actually name or illustrate the compound is *In re Petering*, 301 F.2d 676, 133 USPQ 275 (CCPA 1962), where a disclosed preferred generic class consisting of only about 20 compounds (including the claimed compound) was found to sufficiently "describe" the compound to anticipate. However, one of ordinary skill in the art must be able to draw the structural formula or write the name of each of the compounds included in the generic formula before any of the compounds can be "at once envisaged" and thus anticipated by the reference. MPEP 2131.02[1].

[1] 8th Edition, Rev. 6 at page 2100-69 (August 2007).

Applying *Petering* to the present circumstance, there are hundreds of angiogenesis inhibitors specifically named in the Stokes *et al.* reference and many hundreds of chemotherapeutic agents encompassed by the disclosed genus, subgenus and exemplary species, yielding many thousands of potential specific combinations, far outside of the 20 compounds within the very limited genus of *In re Petering*.

It is therefore respectfully submitted that the generic disclosure of "conjoint" treatment in the Stokes *et al.* reference does not even come close to meeting the very narrow genus criteria set out in *In re Petering*, and clearly is not sufficiently descriptive of the presently claimed combination to constitute an anticipation thereof. It is therefore requested that this anticipation ground for rejection be withdrawn.

Claim rejections - 35 USC 103(a)

Claims 10 and 19-23 are also rejected under 103(a) as being unpatentable over Stokes *et al.* (WO '212 and corresponding US '800). The Examiner references and incorporates by reference the discussion of Stokes *et al.* in connection with the rejection under 102(b), and additionally comments:

> To reiterate in part, Stokes et al. (US Patent 7,074,800) teach compositions comprising certain angiogenesis inhibitors, including AZD2171, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable excipient or carrier (see reference claims 12, and 25). Stokes et al. teach antigangiogenic compounds, including AZD2171 (see reference claim 12), or pharmaceutically acceptable salts, for use in the manufacture of medicament for producing an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human being (see also col. 62, lines 1-35). Stokes et al. teach that in the field of oncology, it is normal practice to use a combination of different forms of treatment to treat each patient with cancer (col. 62, lines 42-45). Stokes et al. teach that conjoint treatment with surgery, radiotherapy or chemotherapy may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment (col. 62, line 36 to col. 63, line 32, especially, col. 62, lines 40-42). In particular, Stokes et al. disclose antiproliferative/antineoplastic agents such as taxoid like taxol and taxotere to be suitable for use in combination with said antiangiogenic compounds (col. 63, lines 11-32, especially line 23).
>
> Based on the teaching of Stokes, someone of skill in the art would have been motivated to create the instant claimed inventive concept.

> Thus, someone of skill in the art at the time the instant invention was made would have found it obvious to create the instant claimed invention with reasonable predictability.

This ground for rejection is respectfully traversed. In response to this rejection, the Examiner's attention is called to the above discussion of Stokes *et al.* (which is incorporated here by reference) and the following additional comments.

As detailed above, Stokes *et al.* describes many compounds of formula I of which AZD2171 is but one, and Stokes *et al.* then notes that compounds of formula I may also be applied in a conjoint treatment with a very long list of various types of chemotherapeutic agents. The number of individual combinations possible from selecting from the two lists is immense.

No guidance or preference is expressed in context of such conjoint treatment for the combination of any particular compound of formula I with any particular chemotherapeutic agent there listed, except possibly the statement at column 63, lines 34-39, that such conjoint treatment may be achieved by administration of "a compound of formula I as defined hereinbefore, and a vascular targeting agent described in WO 99/02166 such as N-acetylcolchinol-O-phosphate (Example 1 of WO 99/02166)." This clearly does not suggest the presently claimed invention and, if anything, would the guide the skilled person *away* from the specific combination of AZD2171 and a taxane.

Moreover, as noted in the present application at page 3, lines 26-27, nowhere in Stokes *et al* does it state that use of any compound of the invention therein with other treatments will produce surprisingly beneficial effects. However, the data given on pages 18-19 and in Figures 1 and 2 of the present application show that the use of AZD2171 in combination with docetaxel unexpectedly produces a significantly greater effect against the tumour than either AZD2171 or docetaxel used alone, in particular, the use of AZD2171 in combination with docetaxel unexpectedly produced a statistically significant *decrease* in tumour size, as is evident from Figures 1 and 2 as discussed further below.

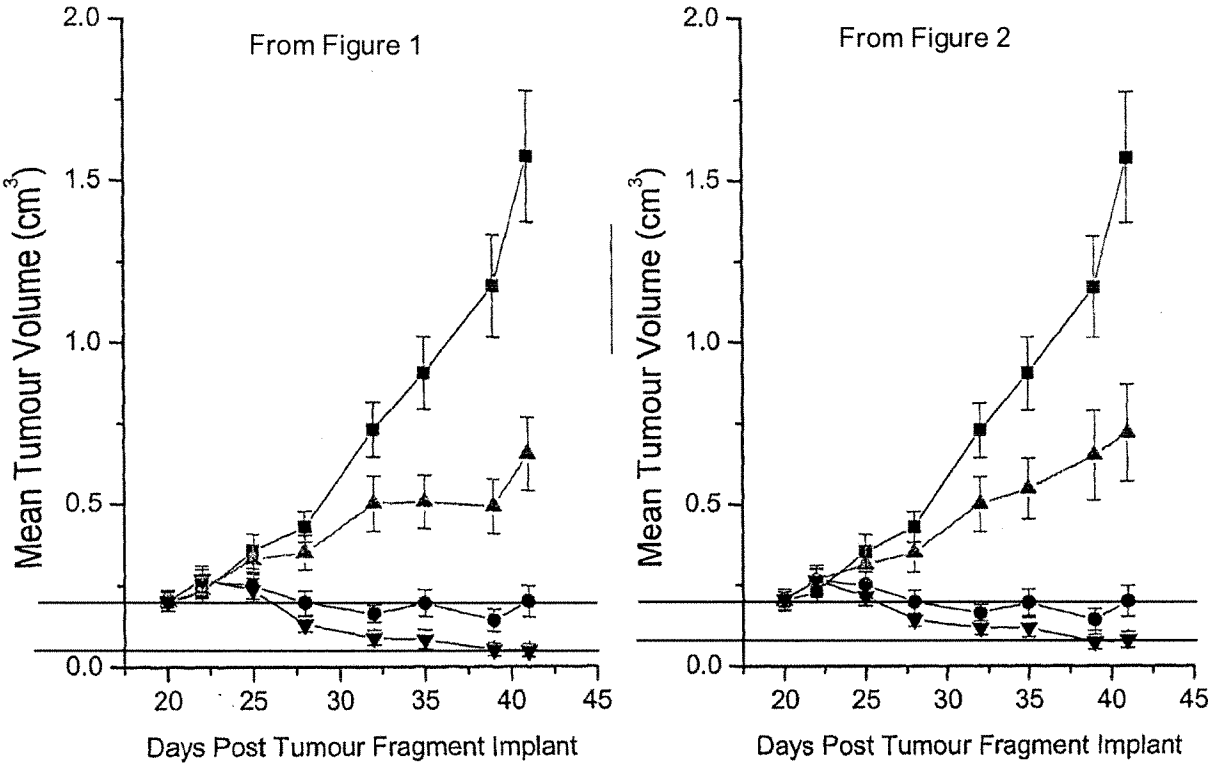
Thus, in the comparative test described on specification pages 18 and 19 using the MX-1 human breast tumour xenograft model, growth inhibition of implanted tumours during the treatment period was determined and compared for the group of animals receiving docetaxel plus AZD2171 against the groups of animals receiving AZD2171 alone and docetaxel alone and a

control group. The results are graphically illustrated in Figures 1 and 2 to the specification. Two sets of comparative tests were conducted, one using 3mg/kg AZD2171 and 10mg/kg docetaxel (Figure 1) and the other using 1.5mg/kg AZD2171 and 10mg/kg docetaxel (Figure 2). As can be clearly seen from both Figures 1 and 2, the combination of AZD2171 and docetaxel produced an unexpected significantly greater tumour inhibition effect than either AZD2171 or docetaxel used alone, and in fact the combination in these tests resulted in a statistically significant *decrease* in tumour size, as compared to either of the agents used alone.

This decrease in tumour size can be seen from Figures 1 and 2 in the specification, and the data points used in preparing Figures 1 and 2 are presented in the following table:

Test	Time post tumour cell injection (days)	20	22	25	28	32	35	39	41
Vehicle	Mean tumour volume (mm^3)	202.13	229.71	353.70	429.71	730.79	905.00	1174.41	1576.08
	SD	113.65	125.89	205.58	183.32	326.95	433.68	612.51	787.77
AZD2171, 3 mg/kg	Mean tumour volume (mm^3)	200.15	237.14	330.66	350.38	501.42	505.64	492.72	653.76
	SD	111.73	147.89	174.97	195.61	323.40	309.58	312.66	426.13
AZD2171, 1.5 mg/kg	Mean tumour volume (mm^3)	202.16	264.17	314.76	352.84	501.69	548.54	651.68	721.66
	SD	111.10	152.34	195.10	230.92	324.69	350.18	527.49	562.98
AZD2171, 3 mg/kg + Docetaxel, 10 mg/kg	Mean tumour volume (mm^3)	202.61	269.20	236.74	131.19	88.55	83.31	52.05	48.80
	SD	113.44	154.22	138.29	91.29	90.68	111.06	74.26	74.68
AZD2171, 1.5 mg/kg + Docetaxel, 10 mg/kg	Mean tumour volume (mm^3)	206.34	265.58	214.85	142.35	117.94	118.28	73.32	79.49
	SD	124.45	178.27	111.35	75.80	79.60	110.47	77.95	88.83
Docetaxel, 10 mg/kg	Mean tumour volume (mm^3)	206.52	264.74	250.16	197.25	163.21	195.00	142.27	200.90
	SD	124.62	130.46	158.15	144.93	100.75	159.90	131.20	183.87

This decrease in tumour size resulting from administration of the combination can clearly be seen from the below copies of Figures 1 and 2 from the specification, on which horizontal lines have been superimposed -- the upper line representing the initial tumour size and the lower line representing the decreased tumour size resulting from administration of the combination.



A declaration verifying the data on the above table, and the statistical significance of this data in demonstrating the decrease in tumour size from administration of the combination, will be provided to the Examiner when it is available to the undersigned after the Holidays. If for some reason the Examiner is unable to locate such declaration in the file at the time this application is taken up for a further Action in the merits, it is respectfully requested that the Examiner telephone the undersigned.

The unexpected beneficial results obtained from the presently claimed combination and shown by the above-noted comparative test results reported in the specification and figures, are also verified and supplemented by the attached publications relating to studies in lung cancer models, which also show that a combination of AZD2171 and a taxane produces surprisingly beneficial effects compared to either agent when used alone. These documents are as follows, with a brief summary of their relevant findings:

Wu PP, Fujitaka K, Mandal J, Imagumbai T Ryan A, Jurgensmeier J Fidler IJ, O'Reilly MS and Herbst RS, AZD2171, an oral, highly potent VEGFR signaling inhibitor, in combination with gefitinib or paclitaxel: results of a study in an orthotopic human lung aclenocarcinoma model. Clin Cancer Res 2005;11: abstract B7.

Wu *et al.* compares treatment of AZD2171 and paclitaxel alone with a combination of AZD2171 and paclitaxel. The Examiner's attention is drawn to the table on the second page of the abstract where it can be seen that the combination shows surprisingly beneficial effects across all the parameters measured in the study. For example the combination resulted in tumour weights of nearly one third that of AZD2171 alone and less than one fifth that of paclitaxel alone and the combination resulted in lymph node metastasis of one fifth that of AZD2171 alone and over one third that of paclitaxel alone.

Furutani K Komaki R, Kuwai T, Jacoby JJ, Korshunova MV, Erez B, Ryan A, Jurgensmeier JM, Herbst RS, O'Reilly MS. Cedirarab, an orally available and highly potent VEGFR signaling inhibitor, inhibits angiogenesis and progression and enhances the effects of paclitaxel in orthotopic human lung adenocarcinoma models. Mol Cancer Ther 2007;6 abstract 425.

Furutani *et al.* compares treatment of AZD2171 and paclitaxel alone with a combination of AZD2171 and paclitaxel. The Examiner's attention is drawn to Tables 1 and 2 and Figure 2 in the poster. Here it can be seen that combined treatment produced significantly decreased lung tumour burden compared to either agent alone and the combination produced significantly decreased lung cancer cell proliferation and enhanced tumour cell apoptosis compared to either agent alone.

Furutani K, Komaki R, Imagumbai T, Onn A, Jacoby JJ, Massarelli E, Korsliunoya MK, Ryan A, Eirgensineier JM, Herbst RS, O'Reilly MS, Targeted therapy against VEGFR-1, -2, and -3 by AZD2171 blocks tumor growth and angiogenesis, and enhances paclitaxel efficacy in an orthotopic lung cancer model. Proc Am Assoc Cancer Res 2007: abstract 2121.

Furutani *et al.* compares treatment of AZD2171 and paclitaxel alone with a combination of AZD2171 and paclitaxel. The Examiner's attention is drawn to the table on the second page of the abstract. Here it can be seen that the combination resulted in a near compete prevention of lung tumour growth in two different lung cancer models superior to either agent alone.

It is respectfully submitted that *even if* a person skilled in the art were to somehow include the presently claimed combination among those to try from the vast number of combinations generically disclosed by Stokes *et al*, such person could not have had any expectation that any particular combination would have such surprisingly significant beneficial effects. Therefore, it is respectfully submitted that even if a case of *prima facie* obviousness were to be made, such *prima facie* obviousness is overcome by the surprisingly significant beneficial results demonstrated by the data in the specification and verified by the test results reported in the subsequent publications noted above. It is therefore respectfully requested that this obviousness ground for rejection be withdrawn.

Nonstatutory Obviousness-Type Double-Patenting

Claims 10, 19-23 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 7 of copending application 10/563,439; claim 11 of copending application 11/663,912; claims 1-9 and 13-14 of copending application 11/994,824; claim 17 of copending application 10/594,235; and claims 9 and 11 of copending application 10/594,233, in view of Stokes *et al.* (WO 00/47212; equivalent to US Patent 7,074,800). The Examiner asserts that "although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are either anticipated by, or would have been obvious in view of the referenced claims." Apparently the Examiner's reasoning is that "each of the above cited copending applications are directed to compositions comprising AZD2171" and, when taken in view of Stokes *et al.*, "claims 10 and 19-23 [of the present application] are deemed to be obvious variants of the limitations of the claimed subject matter of the above cited copending applications in view of Stokes *et al.*"

As the Examiner notes, these rejections are provisional obviousness-type double patenting rejections because the conflicting claims of the copending applications have not in fact been patented. Therefore, although the undersigned disagrees with the Examiner's reasoning regardless of what claims may issue in these referenced applications, arguments against this rejection will be deferred until one or more of such applications is patented, if before allowance of the claims in the present application.

Information Disclosure Statement

The Examiner's attention is called to the Information Disclosure Statement being submitted herewith, which includes a form PTO-1449 and a copy of each of the non-US patent/published application documents, as well as a copy of the International Search Report and the International Preliminary Examination Report. Each of the documents cited in the International Search Report is cited on the form PTO-1449 and a copy is provided therewith. The form PTO-1449 also lists the published US applications and corresponding published PCT applications cited on the Table of related cases of Applicant's assignee provided below, and a copy of the cited published PCT applications is provided with the Information Disclosure Statement.

Technically Related Pending Applications of Applicant's Assignee

The Examiner's attention is called to the following Tables of pending U.S. applications of Applicant's assignee that may be considered technically related to the present invention insofar as they each claim combination therapy involving one or the other of AZD2171 and a taxane with another different therapeutic agent.

The applications on the first Table claim a combination of AZD2171 with another therapeutic agent identified under the heading "Combination." The current status of each application as reported in the PAIR database is given in the right-hand column. Each of the published US applications and PCT applications is listed on the form PTO-1449 attached to the Information Disclosure Statement being submitted herewith, and a copy of each listed published PCT application is provided with the Information Disclosure Statement.

It is assumed that the Examiner has ready electronic access to each of the listed US applications, but the undersigned will provide a copy of any document from these files if requested by the Examiner.

Applications Claiming AZD2171 with Another Therapeutic Agent

US Appln	Date US Filed	US Pub. #	PCT Pub. #	Combination with	Current Status
10/240,413	01 Oct 2002	US 2003 0144298	WO 2001/74360	Anti-hypertensive	Assigned to Examiner Charlesworth E Rae in GAU 1611; Final Rejection Mailed 10-03-2008
10/563,440	05 Jan 2006	US 2006 0160775	WO 2005/004871	ZD6126	Assigned to Examiner Chris E Simmons in GAU 1612; Final Rejection Mailed 07-22-2008
10/563,439	05 Jan 2006	US 2006-0167024	WO 2005/004872	ZD1839	Assigned to Examiner Benjamin J Packard in GAU 1612; Non Final Action Mailed 09-10-2008
10/594,233	25 Sep 2006	US 2008-0125447	WO 2005/092303	CPT-11 and/or 5-FU	Assigned to Examiner Shyam Nathan in GAU 4161; Non-Final Action Mailed 29-Oct-2008
10/594,235	25 Sep 2006	US 2008 0113039	WO 2005/092384	Platinum anti-tumour agent, optionally IR	Assigned to Examiner Shyam Nathan in GAU 4161; Non Final Action Mailed 10-03-2008
11/663,912	27 Mar 2007	US 2008 0015205	WO 2006/035203	Imatinib [Gleevec]	Assigned to Examiner James D. Anderson in GAU 1614; Non Final Action Mailed 09-22-2008
11/994,824	04 Jan 2008		WO 2007/003933	Gemcitabane [Gemzar]	Application Undergoing Preexam Processing; Not yet assigned or published
12/158,266	19 Jun 2008		WO 2007/071970	pemetrexed	Assigned to GAU 1614, no Examiner assigned; predicted first Action 39 months.

The application on the second Table claims a combination of a taxane with another therapeutic agent identified under the heading "Combination." The current status of this application as reported in the PAIR database is given in the right-hand column. The published US application and PCT application are listed on the form PTO-1449 attached to the Information Disclosure Statement being submitted herewith, and a copy of the listed published PCT application is provided with the Information Disclosure Statement.

Again, it is assumed that the Examiner has ready electronic access to this pending US application, but the undersigned will provide a copy of any document from these files if requested by the Examiner.

Applications Claiming a taxane with Another Therapeutic Agent

US Appl	Date US Filed	US Pub #	PCT Pub #	Combination with	Current Status
10/494,704	19-Oct-2004	US 2005-0043395	WO2003/039551	ZD6474	Pending before Examiner Pagonaksis, GAU 1614; Final rejection mailed August 25, 2008

Conclusion

All grounds for rejection having been addressed and, it is believed, by the above amendments, remarks and attachments hereto, this application should now be in condition for allowance, and a Notice to that effect is respectfully requested. However, if there remain any outstanding issues, it is respectfully requested that the Examiner telephone the undersigned at the number given below in order to expedite the resolution of such issues.

EXCEPT for issue fees payable under 37 C.F.R. § 1.18, the Director is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully Submitted,
Morgan Lewis & Bockius LLP

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NCI 2005
Wu et al abstract
FINAL

AZD2171, an oral, highly potent VEGFR signaling inhibitor, in combination with gefitinib or paclitaxel: results of a study in an orthotopic human lung adenocarcinoma model

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Introduction: Lung cancer is a leading cause of cancer death worldwide and the current treatment options available to patients with advanced disease remain limited. Targeted therapy directed against vascular endothelial growth factor (VEGF) or its receptors (VEGFRs) have shown great promise in the clinic as part of the management of lung and other cancers. AZD2171 is an oral, highly potent inhibitor of VEGFR tyrosine kinases. In the current study, we tested AZD2171 alone and in combination with the EGFR inhibitor gefitinib (IRESSA) or with cytotoxic chemotherapy (paclitaxel) in an orthotopic model of human lung cancer.

Methods: *In vivo* assessments were performed using an orthotopic lung adenocarcinoma (NCI-H441) mouse model, which closely mimics the patterns of growth and metastasis observed in man. Five days after tumor cells were implanted into the lungs, mice received one of the following treatments: AZD2171 (6 mg/kg/day p.o.); gefitinib (25 mg/kg/day p.o.); paclitaxel (150 µg/weekly i.p.); AZD2171 plus gefitinib; AZD2171 plus paclitaxel; or vehicle. The experiment was terminated when the control group began to show signs of the onset of morbidity, at which point all animals were sacrificed and assessed for tumor size, pleural effusion, and lymphatic metastasis, and tumor tissues were characterized by immunohistochemical studies.

Results: The suppression of tumor growth, lymphatic and chest wall metastasis, and pleural effusion in the orthotopic lung model was greater in mice treated with AZD2171 plus gefitinib or paclitaxel, compared with each agent as monotherapy (Table).

	Control	Paclitaxel	AZD2171	Gefitinib	AZD2171 + paclitaxel	AZD2171 + gefitinib
Lung tumor (g)	0.32 ± 0.05	0.26 ± 0.09	0.13 ± 0.03 [b]	0.11 ± 0.04 [b]	0.05 ± 0.02 [b]	0.02 ± 0.01 [b]
Pleural effusion (μl)	281 ± 107	133 ± 50	11 ± 3 [a]	65 ± 50 [a]	0 [a]	0 [a]
No. of pleural tumors	8.1 ± 1.2	6.0 ± 2.3	4.9 ± 1.0	4.8 ± 1.9	1.7 ± 1.2 [b]	3.1 ± 0.8 [b]
Incidence of LN metastasis (%)	100	70	100	60	20	50

(a: $p<0.05$; b: $p<0.01$, according to the Student's two-tailed t-test)

Immunohistochemical studies of lung primary tumors revealed that microvessel density, cell proliferation, and levels of proangiogenic factors (VEGF, b-FGF, TGF-α and IL-8) and invasive molecules (MMP-2 and MMP-9) were substantially reduced by treatment with AZD2171 plus gefitinib or paclitaxel.

Conclusions: These data show that AZD2171 produces significant antivascular and antitumor effects in an orthotopic human lung adenocarcinoma model. Combining AZD2171 with the EGFR inhibitor gefitinib or with paclitaxel enhanced the anti-vascular and anti-tumor effects. These studies provide a strong basis for the design of clinical trials in lung cancer patients.

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Targeted therapy against VEGFR-1, -2, and -3 by AZD2171 blocks tumor growth and angiogenesis, and enhances paclitaxel efficacy in an orthotopic lung cancer model

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Introduction: Targeted therapies against vascular endothelial growth factor (VEGF) signaling are currently being evaluated as a therapeutic approach for lung cancer. AZD2171 is a potent orally available small molecule tyrosine kinase inhibitor of VEGF receptors (VEGFR) -1, -2, and -3 that blocks angiogenesis and tumor growth. However, preclinical and clinical data suggest that antiangiogenic agents should be combined with conventional therapy for optimal treatment of advanced malignancies. We therefore evaluated the antitumor and antiangiogenic effects of AZD2171 alone or combined with paclitaxel in an orthotopic mouse model of human lung cancer.

Methods: Studies were performed in an orthotopic lung cancer model that closely mimics clinical patterns of lung cancer growth. Human lung adenocarcinoma cells (PC14) were injected into the left lungs of nude mice with lung tumors evident within 14 days. Mice (10/group) were randomized on day 14 after injection to treatment with AZD2171 (6 mg/kg/day po), paclitaxel (200 μg weekly ip), AZD2171 and paclitaxel, or vehicle. The experiment was terminated when control mice showed signs of morbidity.

All animals were then sacrificed and assessed for tumor burden, pleural effusion and lymphatic metastasis. Tumor tissues were then subjected to immunohistochemical (IHC) analyses.

Results: AZD2171 treatment significantly reduced lung tumor burden ($P<0.001$) with an 87 or 72% reduction in median primary lung tumor volume or total lung weight, respectively, and prevention of mediastinal adenopathy and pleural effusion relative to control. The antitumor and antimetastatic effects of AZD2171 were enhanced when it was combined with paclitaxel. Median lung weight was decreased by 31% by paclitaxel versus 80% by paclitaxel and AZD2171, and lung tumor volume was decreased by 55% by paclitaxel versus 97% by AZD2171 and paclitaxel compared to control ($P<0.001$). IHC analyses reveal that tumor-associated endothelial cells, but not tumor cells, express VEGFR-2 and that VEGFR-2 activation is blocked by AZD2171 therapy alone or in combination with paclitaxel in lung tumors. Microvessel density and tumor cell proliferation in lung tumors was most reduced in the combined therapy group. Combined therapy with AZD2171 and paclitaxel enhanced tumor and tumor-associated endothelial cell apoptosis as compared to either treatment alone.

Conclusions: These data demonstrate that VEGF-receptor signaling blockade by AZD2171 inhibits tumor growth and angiogenesis in an orthotopic human lung adenocarcinoma model. The antitumor and antivascular effects of AZD2171 were substantially enhanced when AZD2171 was combined with paclitaxel. These findings provide support for continued study of AZD2171 with cytotoxic therapies and provide a basis for clinical trials of VEGFR blockade with chemotherapy.

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Targeted therapy against VEGFR-1, -2, an angiogenesis, and enhances paclitaxel e

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Introduction

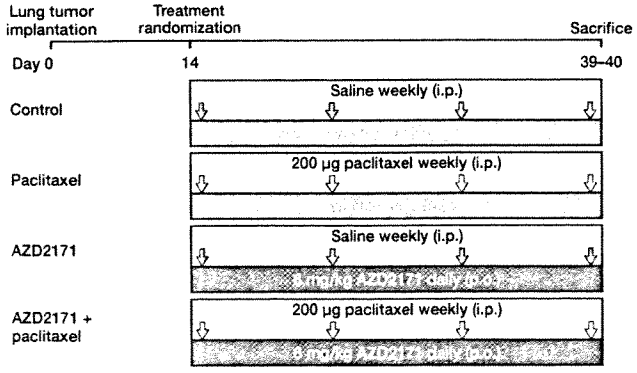
- Conventional treatment of advanced lung cancer offers only limited benefit. Alternative therapeutic strategies are currently under investigation, including novel agents that target angiogenesis and tumor vasculature.
- Vascular endothelial growth factor (VEGF) and its receptors play crucial roles in tumor angiogenesis and growth. AZD2171 (RECENTIN™) is an oral, highly potent and selective VEGF signaling inhibitor of all three VEGF receptors (VEGFR-1, -2, and -3) that prevents angiogenesis and inhibits tumor growth.[1,2]
- Preclinical and clinical data suggest that monotherapy with antiangiogenic agents may not be sufficient for treatment of advanced malignancies and that angiogenesis inhibitors can be usefully combined with conventional therapy.
- The purpose of the current study was to evaluate the antitumor and antiangiogenic effects of AZD2171 alone or in combination with paclitaxel in an orthotopic mouse model of human lung cancer that closely mimics patterns of growth observed in the clinic.

Methods

In vivo tumor model

- Suspensions of PC14 human lung adenocarcinoma cells were prepared in phosphate-buffered saline and growth factor-reduced Matrigel and injected percutaneously into the left lungs of nude mice.
- After 14 days of tumor growth, mice (n=10/group) were randomized to the following treatment groups (Figure 1):
  - Control group: daily vehicle (1% w/v aqueous polysorbate 80 p.o.) and weekly saline i.p.
  - Paclitaxel group: daily vehicle p.o. plus weekly paclitaxel (200 µg i.p.)
  - AZD2171 group: daily AZD2171 (6 mg/kg/day p.o.) plus weekly saline i.p.
  - Combination group: daily AZD2171 (6 mg/kg/day p.o.) plus weekly paclitaxel (200 µg i.p.)

Figure 1. Study design. Treatment was initiated on day 14 after tumor cell injection (tumor growth was confirmed in a cohort of five mice). The experiment was terminated when control mice showed signs of morbidity



- Oral gavages of AZD2171 or vehicle were given in the morning every day.
- Intraperitoneal injections of paclitaxel or saline were given 6 hours after the oral gavages once weekly.
- Mice were sacrificed when controls showed signs of morbidity. Tumor incidence, tumor size, tumor burden (combined weight of the lung and mediastinal tissues), pleural effusion volume, and the incidence of mediastinal and/or distant metastasis were determined.

Immunohistochemistry

- Excised tumors and adjacent tissues were frozen or formalin-fixed.
- Sectioned formalin-fixed, paraffin-embedded tissues were used to detect expression of Ki-67 (proliferation), VEGF and VEGFR-2.
- CD31 expression was determined in frozen tissue sections using a rat anti-mouse CD31 monoclonal antibody.
- Dual fluorescence immunohistochemistry was performed for CD31 and TUNEL (apoptosis), CD31 and VEGFR-2 expression, or CD31 and VEGFR-2 activation (phosphorylation).

Statistical analysis

- Statistical differences were detected using the Mann-Whitney U test.

Results

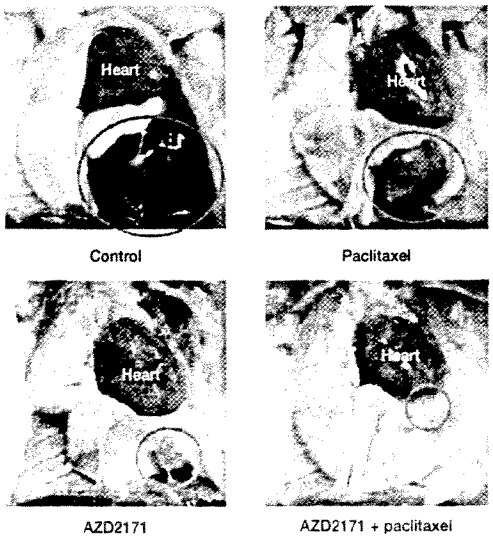
- Treatment with either AZD2171 (6 mg/kg/day p.o.) or paclitaxel (200 µg weekly i.p.) decreased lung tumor volume.
- Combined therapy with AZD2171 and paclitaxel significantly decreased lung tumor burden compared with either agent alone, and prevented mediastinal and systemic metastasis without evidence of toxicity (Table 1 and Figure 2).
- AZD2171 alone and in combination with paclitaxel blocked pleural effusion formation almost completely (Table 1). Paclitaxel alone had an intermediate effect.

Table 1. Treatment of orthotopic human lung adenocarcinomas in mice with AZD2171 and/or paclitaxel. These data were obtained from tissues taken on the day of sacrifice

Treatment	Body weight (g) Median (range)	Tumor incidence	Lung weight (mg) Median (range)	Tumor volume (mm^3) Median (range)	Mediastinal lymph node metastasis	Pleural effusion (µl) Median (range)	Distant metastasis
Control	26.7 (22.8–34.5)	10/10	1176 (488–1659)	1148 (539–1946)	6/10	550 (450–1000)	1/10*
Paclitaxel	31.0 (25.1–39.8)	10/10	808 (284–1392)	516 (18–1593)	4/10	30 (0–960)	0/10
AZD2171	31.2 (25.6–34.1)	10/10	331 (283–475)	148 (73–354)	1/10	0 (0–0.45)	0/10
AZD2171 + paclitaxel	28.4 (23.9–33.2)	10/10	230 (193–248)†	35 (4–127)‡	0/10§	0 (0–0.02)¶	0/10

Left adrenal metastasis; †P<0.001 vs control, paclitaxel or AZD2171; ‡P<0.01 vs control, paclitaxel or AZD2171; §P<0.05 vs control; ¶P<0.01 vs control or paclitaxel

Figure 2. Treatment of orthotopic human lung adenocarcinomas in mice with AZD2171 and/or paclitaxel. The anterior chest wall was removed at the time of sacrifice. The primary tumor in the left lung of a representative mouse from each group is shown



- Combined therapy with AZD2171 and paclitaxel resulted in significantly decreased lung cancer cell proliferation and enhanced tumor cell apoptosis compared with either agent alone, and effectively blocked lung cancer angiogenesis, as measured by microvessel density (MVD; Table 2).
- Immunohistochemical analyses demonstrate that:
  - Human lung adenocarcinoma cells growing in the lung express high levels of VEGF but not VEGFR-2 (Figure 3).
  - Tumor-associated endothelial cells highly express VEGFR-2 (Figure 4).

-3 by AZD2171 blocks tumor growth and ficacy in an orthotopic lung cancer model

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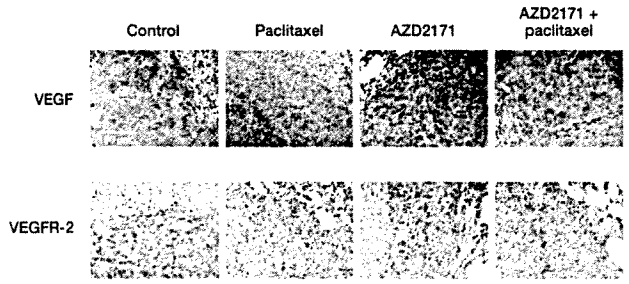
Table 2. Immunohistochemical analyses for microvessel density (CD31), proliferation (Ki67) and apoptosis (TUNEL) in orthotopic human lung adenocarcinomas in mice after treatment with AZD2171 and/or paclitaxel

Treatment	MVD (CD31)	Tumor cells		Endothelial cells
		Proliferation (Ki67)	Apoptosis (TUNEL)	Apoptosis (TUNEL)
Control	15 ± 1	16 ± 1	1 ± 0	0 ± 0
Paclitaxel	12 ± 1	13 ± 1	5 ± 1	1 ± 0
AZD2171	7 ± 1*	7 ± 1*	4 ± 1†	4 ± 1‡
AZD2171 + paclitaxel	4 ± 1§	5 ± 1#	10 ± 1¶	7 ± 2‡

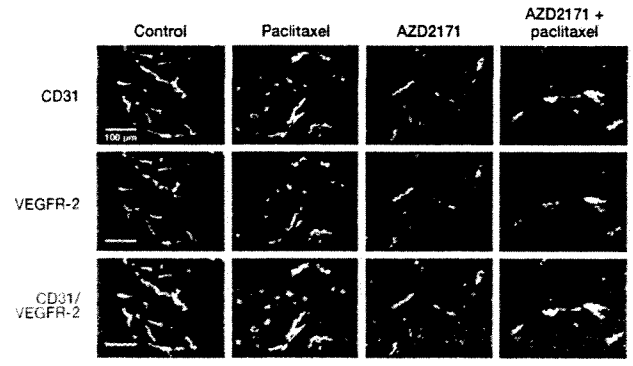
MVD, proliferation and apoptosis values were obtained from 10 random fields (x100 magnification) per tumor
Data are shown as mean ± standard error
**P<0.001 vs control or paclitaxel*
†P<0.001 vs control
‡P<0.005 vs control; P<0.05 vs paclitaxel
§P<0.001 vs control, paclitaxel or AZD2171
¶P<0.001 vs control or paclitaxel; P<0.005 vs AZD2171

Figure 3. Expression of VEGF and VEGFR-2 in orthotopic lung adenocarcinomas from mice treated with AZD2171 and/or paclitaxel



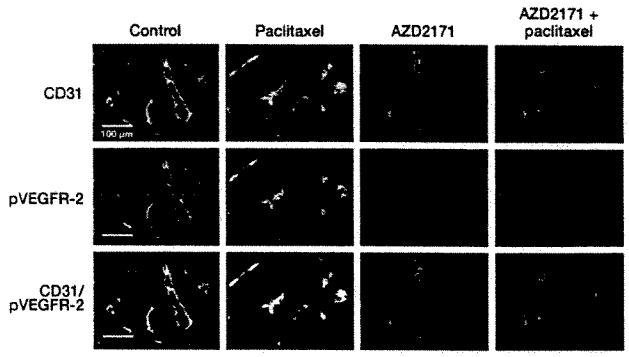
- Treatment with AZD2171 alone or in combination with paclitaxel was associated with a decrease in MVD but did not substantially impact endothelial cell expression of VEGFR-2 (Figure 4).
- However, AZD2171 alone and in combination with paclitaxel blocked activation of VEGFR-2 (measured as pVEGFR-2) in tumor-associated endothelial cells (Figure 5).
- Endothelial cell apoptosis in the lung primary tumors was substantially increased in mice treated with AZD2171 alone and in combination with paclitaxel compared with mice treated with paclitaxel alone or vehicle control (Figure 6).

Figure 4. Endothelial expression of VEGFR-2 in orthotopic lung adenocarcinomas from mice treated with AZD2171 and/or paclitaxel



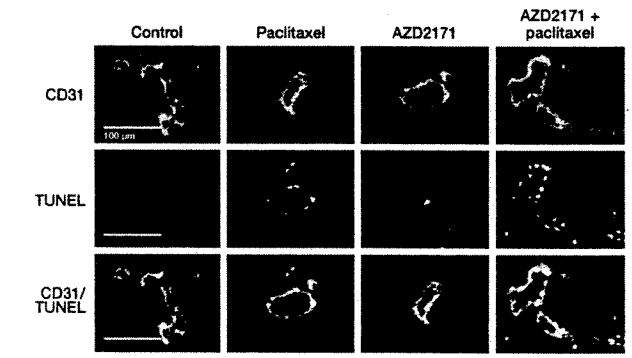
Fluorescent red, CD31-positive endothelial cells; fluorescent green, VEGFR-2-positive cells; fluorescent yellow, VEGFR-2-positive tumor-associated endothelial cells

Figure 5. Activation of VEGFR-2 in endothelial cells in orthotopic lung adenocarcinomas from mice treated with AZD2171 and/or paclitaxel



Fluorescent red, CD31-positive endothelial cells; fluorescent green, pVEGFR-2-positive cells; fluorescent yellow, pVEGFR-2-positive tumor-associated endothelial cells

Figure 6. Apoptosis of endothelial cells in orthotopic lung adenocarcinomas from mice treated with AZD2171 and/or paclitaxel



Fluorescent red, CD31-positive endothelial cells; fluorescent green, apoptotic cells; fluorescent yellow, apoptotic tumor-associated endothelial cells

Conclusions

- VEGFR signaling is an attractive therapeutic target in lung cancer. For patients with advanced disease, VEGFR signaling inhibitors may be combined with conventional modalities.
- Our current studies reveal that the antiangiogenic and antivascular effects of AZD2171, a highly potent and selective signaling inhibitor of all three VEGFRs, improved the antitumor efficacy of chemotherapy, blocked pleural effusion formation and metastasis in an orthotopic mouse model of human lung adenocarcinoma.
- These data strongly support the continued evaluation of AZD2171 in combination with cytotoxic therapies and suggest that it may be useful to combine AZD2171 and chemotherapy as part of the multimodality management of lung cancer.

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RECENTIN Furutani et al abstract
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Cediranib, an orally available and highly potent VEGFR signaling inhibitor, inhibits angiogenesis and progression and enhances the effects of paclitaxel in orthotopic human lung adenocarcinoma models

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Introduction: Lung cancer is a leading cause of cancer death and conventional treatments have reached a therapeutic plateau. Targeted therapies directed against vascular endothelial growth factor (VEGF) or its receptors (VEGFRs) have shown great promise in the clinic when combined with chemotherapy for lung cancer. In the current study, we evaluated the therapeutic and antiangiogenic effects of cediranib (RECENTIN™; AZD2171), an orally available and highly potent selective inhibitor of all three VEGFR tyrosine kinases, alone and in combination with paclitaxel in slowly or rapidly progressive models of human lung adenocarcinoma.

Methods: Human lung adenocarcinoma cells (PC14-PE6 or NCI-H441) were injected orthotopically into the lungs of mice. Subgroups of mice (n=5) were sacrificed weekly and assessed for the presence of lung tumors. After 2 weeks, when tumors were observed in all mice, the remaining animals (n=10/group) were randomized to treatment with cediranib (6 mg/kg/day orally); paclitaxel (200 μg/mouse/week ip); cediranib plus paclitaxel; or vehicle control. All animals were killed and assessed for lung tumor burden and metastasis when control animals became moribund after 26 (PC14-PE6) or 107

(NCI-H441) days of treatment, and tumor and adjacent normal lung tissues were subjected to immunohistochemical studies.

Results: Cediranib therapy was well tolerated and highly effective in both orthotopic human lung adenocarcinoma models and prevented metastasis. The addition of paclitaxel to cediranib resulted in the near complete prevention of lung tumor growth in both models and was superior to paclitaxel alone (Table). Pleural effusions, which were observed in the PC14-PE6 model, were prevented by cediranib.

Tumor type	Treatment group	Lung weight (mg) median (range)	Tumor volume (mm^3) median (range)	Mediastinal lymph node metastasis (incidence)
PC14-PE6	Vehicle	1176 (488–1659)	1148 (539–1946)	6/10
	Paclitaxel	808 (284–1392)*	516 (18–1593)*	4/10
	Cediranib	331 (283–475)**	148 (73–354)**	1/10
	Cediranib/paclitaxel	230 (193–248)**	35 (4–127)**	0/10*
NCI-H441	Vehicle	1046 (295–1760)	746 (97–1337)	6/10
	Paclitaxel	389 (220–1259)*	194 (20–837)*	7/10
	Cediranib	242 (199–591)**	37 (4–224)**	4/10
	Cediranib/paclitaxel	237 (180–363)**	12 (2–151)**	2/10

$P<0.05$* or 0.001** vs vehicle

Immunohistochemical studies of lung tumors revealed that cediranib did not substantially impact VEGF or VEGFR expression but blocked VEGFR activation in the tumor vasculature. In the NCI-H441 lung tumors, tumor cell expression of VEGFR-2 was also observed and its activation was blocked by cediranib treatment. Lung tumor angiogenesis, as determined by microvessel density, and tumor cell proliferation were blocked and apoptosis was increased by treatment with cediranib alone and in combination with paclitaxel.

Conclusions: These data show that cediranib inhibits tumor angiogenesis and growth in slowly (NCI-H441) and rapidly (PC14-PE6) progressive orthotopic human lung adenocarcinoma models. Combining cediranib with paclitaxel enhanced the antitumor effects with a near complete suppression of tumor growth in the lung and metastasis to the mediastinal nodes. These studies provide a strong basis for the design of clinical trials with cediranib in lung cancer patients.

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